JC03 Rec'd PCT/PTO 02 MAR 2001
09/763616
PCT/AU99/00724
Received 7 July 2000

THE CLAIMS:

1. A method of identifying compounds useful in the treatment of a disease condition caused or exacerbated by an MPV comprising contacting a protein molecule containing a chelated metal cation domain, encoded by an MPV gene, with an effective amount of said compound for a time and under conditions sufficient to facilitate disruption of the chelated metal cation domain and directly or indirectly determining the amount of chelated metal cation released wherein the amount of chelated metal cation released is indicative of the disruption of the chelated metal cation domain.

2. A method according to claim 1 wherein the metal is zinc.

3. A method according to claim 2 wherein the release of zinc is determined by a change in fluorescence of a zinc-selective fluorophore.

4. A method according to claim 3 wherein the fluorophore is TSQ.

5. A method of identifying compounds useful in the treatment of a disease condition caused or exacerbated by an MPV comprising contacting a protein molecule containing a chelated metal cation domain, encoded by an MPV gene, with an effective amount of said compound for a time and under conditions sufficient to facilitate disruption of the chelated metal cation domain and directly or indirectly determining the absence or otherwise of binding of said protein to a ligand, wherein the absence of binding is indicative of disruption of the chelated metal cation domain.

6. A method according to claim 5 wherein the ligand is E6AP, E6BP, paxilin or similar or homologue motifs.

7. A method according to claim 1 or 5 wherein the MPV is an HPV.

8. A method according to claim 7 wherein the HPV is selected from HPV-6, HPV-11, HPV-16, HPV-18.

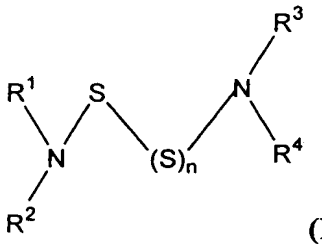
9. A method according to claim 8 wherein the HPV is HPV-16.

10. A method according to claim 9 wherein the protein is the HPV-16 E6 or E7 oncoprotein.

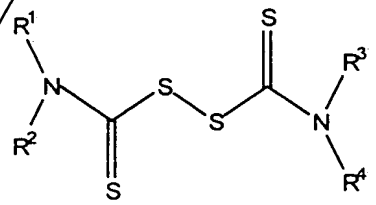
11. A method according to claim 8 wherein the HPV is HPV-18.

12. A method according to claim 11 wherein the protein is the HPV-18 E6 or E7 oncoprotein.

13. A method of treating or preventing a disease condition caused or exacerbated by an MPV comprising the administration of an effective amount of a compound capable of facilitating the disruption of a chelated metal cation domain of a protein encoded for by an MPV gene to a mammal in need thereof, wherein the compound is of general formula (I) or (II):



(I)



(II)

wherein

n is selected from 1-5

R^1 - R^4 are independently selected from hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally

substituted arylalkyl optionally substituted acyl, optionally substituted heterocyclyl, halo alkyl, arylalkyl, carboxy, carboxy ester and carboxamido; or

R^1 and R^2 together, and/or R^3 and R^4 together, independently form a group of formula (a):

$$- (CH_2)_l - U_m - (CH_2)_n - \qquad (a)$$

wherein: U is selected from CH_2, O, NH or S;

l and n are independently selected from 0 to 6 and m is 0 or 1 when U is CH_2 and m is 1 when U is O, NH or S, such that

l+m+n is greater than or equal to 2;

and wherein any one or more (CH_2) or NH groups may be further optionally substituted.

14. A method according to claim 13 wherein R^1 and R^2 together, and/or R^3 and R^4 together, independently form a group of formula (a):

$$- (CH_2)_l - U_m - (CH_2)_n - \qquad (a)$$

wherein: U is selected from CH_2, O, NH or S;

l and n are independently selected from 0 to 6 and m is 0 or 1 when U is CH_2 and m is 1 when U is O, NH or S, such that

l+m+n is greater than or equal to 2;

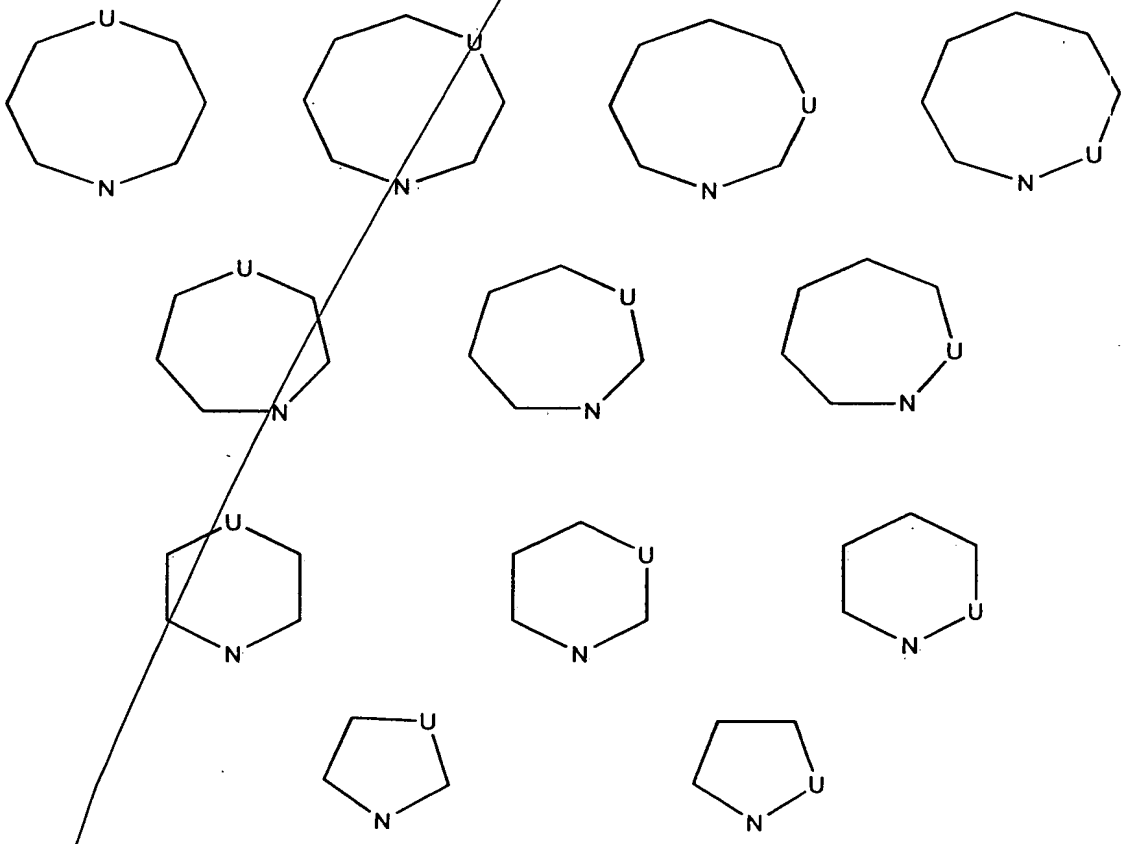
and wherein any one or more (CH_2) or NH groups may be further optionally substituted.

15. A method according to claim 14 wherein U is CH_2.

16. A method according to claim 15 wherein formula (a) is selected from one of -$(CH_2)_2$-, -$(CH_2)_3$-, -$(CH_2)_4$- , -$(CH_2)_5$-, -$(CH_2)_6$- or -$(CH_2)_7$-.

17. A method according to claim 14 wherein U is NH, O, or S and m is 1.

18. A method according to claim 14 wherein R^1 and R^2, and/or R^3 and R^4, together with the nitrogen to which they are attached independently form a group selected from:



which may be optionally substituted at a carbon atom, and/or where U is NH, at the nitrogen atom.

19. A method according to claim 18 wherein R^1 and R^2, and/or R^3 and R^4, together with the nitrogen to which they are attached each independently form an optionally substituted morpholino, thiomorpholino, or piperazino group.

20. A method according to any one of claims 14 ~~to 19~~ wherein any $-CH_2-$ group of formula (a) is optionally substituted by one or more of the groups selected from methyl, ethyl, n-propyl, iso-propyl, hydroxy, halo, methoxy, ethoxy, iso-propoxy, acetoxy, optionally substituted benzyl, optionally substituted pyridyl, optionally substituted pyrimidyl and optionally substituted phenyl.

21. A method according to claim 13 wherein at least one of R^1 - R^4 is independently selected from: hydrogen, optionally substituted phenyl, optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted cyclohexyl, formyl, acetyl.

22. A method according to claim 21 wherein the optional substituent is selected from the groups methyl, ethyl, n-propyl, iso-propyl, hydroxy, halo, methoxy, ethoxy, iso-propoxy, acetoxy, and phenyl.

23. A method according to claim 13 wherein at least one of R^1-R^4 is as depicted in any compound in Groups 1 to 6 as defined herein.

24. A method according to claim 13 wherein n is selected from 1, 2 or 3, preferably 1 or 2.

25. A method according to claim 13 wherein the MPV is an HPV.

26. A method according to claim 25 wherein the HPV is selected from the group consisting of HPV-1, 2, 3, 4, 6, 11, 16, 18, 27, 31, 33, 35, 45 and 57.

27. A method according to claim 26 wherein the HPV is HPV-16.

28. A method according to claim 27 wherein the protein is the HPV-16 E6 or E7 oncoprotein.

29. A method according to claim 26 wherein the HPV is HPV-18.

30. A method according to claim 29 wherein the protein is the HPV-18 E6 or E7 oncoprotein.

31. A method according to claim 13 where the chelated metal cation domain is a chelated zinc cation domain.

32. A method according to claim 31 wherein the chelated zinc domain is the sequence motif cys-X2-cys-X29-cys-X2-cys.

33. A method of treating or preventing a disease condition caused or exacerbated by an MPV comprising the administration of an effective amount of a compound as defined in claim 13 to a mammal in need thereof.

34. A method according to claim 13 ~~or 33~~ wherein the compound is capable of effecting at least 30% zinc release in a TSQ assay and/or inhibits or reduces the binding of an E6 protein to E6AP or E6BP and/or exhibits selective cytotoxicity towards MPV-infected cells.

35. A method according to claim 13 ~~or 33~~ wherein the disease or condition is cervical cancer or its HPV associated precursor lesions or any other HPV associated cancers and/or warts.

36. A composition comprising a compound capable of facilitating the disruption of a chelated metal cation domain of a protein encoded for by an MPV gene, together with a pharmaceutically acceptable carrier, diluent or excipient wherein the compound is of general Formula (I) or (II) as defined in claim 13.

37. Use of a compound capable of facilitating the disruption of a chelated metal cation domain of a protein encoded for by an MPV gene in the manufacture of a medicament for the treatment or prophylaxis of a disease or condition caused or exacerbated by a MPV, wherein the compound is of general Formula (I) or (II) as defined in claim 13.

38. Use of at least one compound of general formula (I) or (II) as defined in claim 13 in the manufacture of a medicament for the treatment or prophylaxis of a disease or condition caused or exacerbated by an MPV.

39. An agent useful in the treatment or prophylaxis of a disease condition caused or exacerbated by an MPV, said agent comprising a compound capable of reducing, inhibiting or otherwise decreasing the activity of a protein encoded by an MPV gene where said agent facilitates disruption of a chelated metal cation domain present in said protein, wherein the compound is of general formula (I) or (II) as defined in claim 13.

40. A method of treating or preventing a disease condition caused or exacerbated by an MPV comprising the administration of an effective amount of a compound capable of facilitating the disruption of a chelated metal cation domain of a protein encoded for by an MPV gene to a mammal in need thereof, wherein said compound is a compound identified in accordance with the method of claim 1.